REMARKS

Status of Claims

Applicants note a discrepancy in the Office Action Summary in which the Examiner indicates that claims 28, 33, and 34 are pending, whereas these claims were, in fact, previously canceled. The pending claims are claims 1, 3, 5, 10, 11, 14, 15, 17-19, 21-24, 27, 29-30, 35-42, 48-59, 61-63, 86-94, and 101-113, of which claims 19, 21-24, 27-30, 33-39, 41 and 111-113 have been withdrawn from consideration. Claims 1, 3, 5, 10, 11, 14, 15, 17, 18, 40, 42, 48-59, 61-63, 86-94 and 101-110 are currently under examination and stand rejected. Claims 101 and 102 are amended herein to specify that the compositions are thermally cross-linked. No new matter is introduced.

Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement filed on December 23, 2009 fails to comply with the provisions of 37 C.F.R. 1.97, 1.98 and MPEP § 609 because no copy of the listed references was provided with that submission. Applicants respectfully point out that the foreign patent publications listed in the December 23, 2009 IDS were previously supplied to the USPTO on June 15, 2009 as indicated on the IDS. Nevertheless, for the Examiner convenience, Applicants resubmit the foreign publications herewith and request that they be considered.

The Examiner has also indicated that it is unclear whether the list of related cases submitted by the Applicants on December 23, 2009 is meant to be an IDS. That a Related Case Submission was filed to bring to the Examiner's attention other applications co-owned by the Applicants. Applicants again submit herewith a Related Case Submission for the Examiner's consideration and make explicit reference to the same in the current IDS.

Claim Rejections

OBVIOUSNESS

Claims 1, 3, 5, 10, 11, 14, 15, 17, 18, 40, 42, 48-59, 61-63, 86-99 and 101-110 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Noishiki (U.S. Patent No. 5,986,168), in view of Choi et al. (*J. Biomed. Mater. Res.*, 1999), Della Valle et al. (U.S. Patent No. 4,851,521), and Moore et al. (U.S. Patent No. 3,678,933). Briefly, the Examiner contends that Noshiki teaches a prosthesis which, according to the Examiner, "can be a wound dressing or hemostats," comprising bioabsorbale substances formed by "thermal crosslinking, and excluding chemical reagents." The Examiner notes that Noishiki "does not particularly teach gelatin and HA" but contends that it would have been "obvious . . . to try gelatin and HA" because these are taught to be bioabsorbable substances and the Examples of Noishiki disclose crosslinking of two different substances. The Examiner relies on Choi as teaching "a hemostatic composition of gelatin and HA" and contends that, based on Choi, one skilled in the art "would certainly try this combination" in Noishiki's prosthesis. The Examiner relies on Della Valle et al. and Moore only with respect to dependent claims. Applicants traverse.

The Examiner's contention that it would have been "obvious to try" to apply Noishiki's thermal cross-linking to Choi's combination of gelatin and HA is erroneous and contrary to the Supreme Court's holding in KSR v. Teleflex, 550 US 398 (2007). In KSR, the Supreme Court clarified the situations in which obviousness might be predicated on the "obvious to try" standard:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103. (emphasis added)

Accordingly, it is only where the results of a modification would be predictable, such that success would have been expected, that the "obvious to try" rationale is applicable. See, In re

Kubin, 561 F.3d 1351 (Fed. Cir. 2009); Ortho–McNeil Pharma. v. Mylan Labs., 520 F.3d 1358 (Fed. Cir. 2008); Eisai Co. v. Dr. Reddy's Labs., 533 F.3d. 1353 (Fed. Cir. 2008); Takeda Chemical Indus. v. Alphapharm, 492 F.3d 1350 (Fed. Cir. 2007); and In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). A finding of obviousness "does not require absolute predictability of success," but there must at least be "a reasonable expectation of success" in making a claimed modification of the prior art. O'Farrell, at 903-04; MPEP § 2143.02(I).

The Examiner makes the conclusory statement the there would have been "a reasonable expectation of success" in combining the teachings of Noishiki's and Choi, but does not make even the most perfunctory effort to explain why one skilled in the art would have such an expectation. Indeed, there simply could not have been a reasonable expectation of success because the art, as a whole, taught away from exposing HA to the elevated temperatures required for thermal cross-linking because, as taught in the instant specification, HA is unstable at high temperatures and therefore it could not have been expected that a composition comprising HA would be active as a hemostat after treatment with heat at 110-200°C. (p. 18, lines 29-32).

The Examiner does not even mention the Min et al. and Fan et al. references discussed in Applicant's previous submission, both of which directly teach away from heating HA to 110-200°C, as specified in independent claims 1, 40, 42, and 103. It is improper for the Examiner to disregard these teachings because the "totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." In re Hedges, 783 F.2d 1038 (Fed. Cir. 1986).

Indeed, in Hedges, a claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures. Of record in the present case, is the article Min et al., "Molecular Weight Changes of Sodium Hyaluronate Powder and Solution by Heat Treatment," Matrix Biology Institute, Proceedings of Hyaluronan, Oct. 11-16, 2003, which teaches that heat treatment leads to significant degradation of HA, that 70°C is the optimal temperature for heat treatment of hyaluronic acid, and that at temperatures higher than 70°C consistent results can not be obtained. Likewise, Fan et al. (U.S. Pub. 2009/0087569), also of record, teaches that "HA is

very unstable" at a "temperature higher than 60°C." ¶ [0003] (emphasis added). Fan further teaches that the conventional wisdom is to modify HA by chemical methods:

> At present there are a great deal [of] researchers trying to modify hyaluronic acid in order to expand its use in the medical field, with most of them applying chemical methods as cross-linking or esterificating maneuvers to improve physical strength or reduce decomposition speed in vivo. ¶ [0006]. (emphasis added)

Even the Noishiki reference recognizes that not all of the bioabsorbable materials should be subjected to the same temperatures. In the Examples, Noishiki teaches crosslinking by thermal heating at 130°C only for specific materials: succinylated collagen (Example 1), succinylated collagen and dermatan sulphate (Example 23), and collagen and heparin (Examples 29 and 30). Noishiki does not suggest that these temperatures are suitable for all of the bioabsorbable materials disclosed in the laundry list spanning column 5, line 66 to column 6, line 6. Rather, Noishiki makes clear that "[t]he heating parameters depend on the type of bioabsorbable substance." (Col. 8, ln. 15-16). In view of Min et al. and Fan et al., Noishiki would thus suggests that some bioabsorbable substances should be treated at lower temperatures or by one of the alternative crosslinking methods taught, such as gamma irradiation, UV irradiation, or hydrously swelling the substance.

The Examiner also ignores the fact that the claimed compositions are haemostatic compositions, whereas the composition of Choi is not intended for control of active bleeding (haemostasis), which is a process that occurs within minutes post-injury, but rather Choi is concerned with wound healing and like processes which occur over several days. The Examiner states that Choi et al. "teach a haemostatic composition of gelatin and HA," but this is incorrect. Choi nowhere mentions the word "haemostatic" and, in fact, relates to a wound dressing for use as artificial skin or a scaffold for tissue engineering. The Examiner will note, for example, that Choi states that wounds are examined "on either the 5th or 12th postoperative day" (Choi et al., p. 634). Hence, Choi clearly does not relate to the control of active bleeding but is instead concerned with the longer term effects on wound healing where new tissue is formed and the wound is closed.

Likewise, the vascular prosthesis of Noishiki provides a physical barrier against bleeding and is intended to promote neointima formation over several days or months (see, e.g., Example 6). Noishiki mentions in passing that the "prosthesis of this invention can be used as cardiac wall prostheses and vascular prostheses, but the substances and the methods to produce them are also applicable in other fields, such as in tissue repair substitutes, wound dressings, and hemostats." (col. 9, lines 17-21). However, there is no data provided to demonstrate efficacy of any of Noishiki's compositions as hemostats, and given the fact that Noishiki does not even disclose a combination of HA and gelatin, let alone a thermally cross-linked combination of HA and gelatin, it cannot be said that this statement would have imbued one skilled in the art with a reasonable expectation that a thermally cross-linked HA-gelatin composite would be a potent hemostat, particularly in view of the contrary teachings in the art.

Even assuming, arguendo, that the one would have applied Noishiki's heat treatment to Choi's combination of gelatin and HA, there still would not have been a reasonable expectation that the resulting composition would function as a hemostatic agent because: (i) the properties of the cross-linked material could not have been predicted in view of the fact that the HA would be expected to degrade significantly, as discussed above, and (ii) as discussed below, other art of record, namely Yannas (U.S. Patent 4,280,954), taught away from including HA in a haemostatic agent.

Specifically, the claimed haemostatic composition, which by definition has pro-coagulant properties, is surprising in view of Yannas, which teaches that compositions comprising HA and collagen have anti-coagulant properties and are compatible with blood, as previously discussed by Applicant. For instance, Examples 12 and 13 of Yannas show that HA-collagen composites fail to exhibit significant differences in whole blood clotting time (WBCT) compared to collagen itself. Even more surprising is the degree of pro-coagulant effect shown by the present invention. For instance, Example 6 of the present application shows that gelatin powder with 10% HA reduces bleeding 1.28 times better than gelatin powder alone (Table on page 32, S3 versus S2), while the gelatin sponge with 30% HA reduces bleeding 5.2 times better than the gelatin sponge without HA (Table on page 32, S4 versus S1). This remarkable result is not contemplated by the prior art, and, in multiple respects, cuts against the teachings and prevailing wisdom in the art.

For at least the forgoing reasons, Applicants respectfully submit that it would not have been obvious to a person of ordinary skill to thermally crosslink a composition comprising gelatin and hyaluronic acid based on the teaching of Noishiki and Choi when considering the state of the art as a whole, which includes teachings that hyaluronic acid should not be subjected to high temperatures and that HA-collagen composites have anti-coagulant properties and are compatible with blood.

Having distinguished the independent claims from the art of record, Applicants submit that the claims dependent therefrom are patentable for at least the same reasons, but reserve the right to separately address the patentability of those claims in the future, should that become necessary. The Examiner has previously indicated that withdrawn method claims 19, 21-24, 27, 29-30, 35-39, and 41 would be rejoined should a product claim was allowed. Applicants believe that the product claims are in condition for allowance and respectfully request rejoinder of the method claims, each of which either depends from the product claims or includes the distinguishing features of the product claims.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendments and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 50-3732, Order No. 13323.105005. Furthermore, in the event that an extension of time is required, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to the above-noted Deposit Account No. 50-3732 and Order No. 13323.105005.

Respectfully submitted,

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Dated: December 21, 2010

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